Mechanoresponsive stem cells to target cancer metastases through biophysical cues.

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Public Summary:
Despite decades of effort, little progress has been made to improve the treatment of cancer metastases. To leverage the central role of the mechanoenvironment in cancer metastasis, we present a mechanoresponsive cell system (MRCS) to selectively identify and treat cancer metastases by targeting the specific biophysical cues in the tumor niche in vivo. Our MRCS uses mechanosensitive promoter-driven mesenchymal stem cell (MSC)-based vectors, which selectively home to and target cancer metastases in response to specific mechanical cues to deliver therapeutics to effectively kill cancer cells, as demonstrated in a metastatic breast cancer mouse model. Our data suggest a strong correlation between collagen cross-linking and increased tissue stiffness at the metastatic sites, where our MRCS is specifically activated by the specific cancer-associated mechano-cues. MRCS has markedly reduced deleterious effects compared to MSCs constitutively expressing therapeutics. MRCS indicates that biophysical cues, specifically matrix stiffness, are appealing targets for cancer treatment due to their long persistence in the body (measured in years), making them refractory to the development of resistance to treatment. Our MRCS can serve as a platform for future diagnostics and therapies targeting aberrant tissue stiffness in conditions such as cancer and fibrotic diseases, and it should help to elucidate mechanobiology and reveal what cells "feel" in the microenvironment in vivo.

Scientific Abstract:
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